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7-24-00

This application claims the benefit of provisional  
application ~~101~~ No. 60/044,692, filed on Apr. 18, 1997.

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5 [ LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE  
SEQUELAE ASSOCIATED WITH PTCA PROCEDURES,  
INCLUDING DELIVERY USING A MODIFIED STENT ]

Field of the Invention:

10 Delivery of rapamycin locally, particularly from an  
intravascular stent, directly from micropores in the stent  
body or mixed or bound to a polymer coating applied on  
stent, to inhibit neointimal tissue proliferation and  
thereby prevent restenosis. This invention also  
15 facilitates the performance of the stent in inhibiting  
restenosis.

Background of the Invention:

20 Re-narrowing (restenosis) of an arteriosclerotic  
coronary artery after percutaneous transluminal coronary  
angioplasty (PTCA) occurs in 10-50% of patients undergoing  
this procedure and subsequently requires either further  
angioplasty or coronary artery bypass graft. While the  
exact hormonal and cellular processes promoting restenosis  
25 are still being determined, our present understanding is  
that the process of PTCA, besides opening the  
arteriosclerotically obstructed artery, also injures  
resident coronary arterial smooth muscle cells (SMC). In  
response to this injury, adhering platelets, infiltrating  
macrophages, leukocytes, or the smooth muscle cells (SMC)  
30 themselves release cell derived growth factors with  
subsequent proliferation and migration of medial SMC  
through the internal elastic lamina to the area of the  
vessel intima. Further proliferation and hyperplasia of

5 intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3-6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

10 Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both *in vitro* and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes *c-fos* and *c-myc*, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequstration of growth regulatory factors such as fibrovalent growth factor (FGF).

25 Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, 30 trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and *c-myc* and *c-myb* antinsense oligonucleotides.

5           Additionally, a goat antibody to the SMC mitogen  
platelet derived growth factor (PDGF) has been shown to be  
effective in reducing myointimal thickening in a rat model  
of balloon angioplasty injury, thereby implicating PDGF  
10           directly in the etiology of restenosis. Thus, while no  
therapy has as yet proven successful clinically in  
preventing restenosis after angioplasty, the *in vivo*  
experimental success of several agents known to inhibit  
SMC growth suggests that these agents as a class have the  
capacity to prevent clinical restenosis and deserve  
15           careful evaluation in humans.

Coronary heart disease is the major cause of death in  
men over the age of 40 and in women over the age of fifty  
20           in the western world. Most coronary artery-related deaths  
are due to atherosclerosis. Atherosclerotic lesions which  
limit or obstruct coronary blood flow are the major cause  
of ischemic heart disease related mortality and result in  
500,000-600,000 deaths in the United States annually. To  
25           arrest the disease process and prevent the more advanced  
disease states in which the cardiac muscle itself is  
compromised, direct intervention has been employed via  
percutaneous transluminal coronary angioplasty (PTCA) or  
coronary artery bypass graft (CABG).

30           PTCA is a procedure in which a small balloon-tipped  
catheter is passed down a narrowed coronary artery and  
then expanded to re-open the artery. It is currently  
performed in approximately 250,000-300,000 patients each

5 year. The major advantage of this therapy is that  
patients in which the procedure is successful need not  
undergo the more invasive surgical procedure of coronary  
artery bypass graft. A major difficulty with PTCA is the  
10 problem of post-angioplasty closure of the vessel, both  
immediately after PTCA (acute reocclusion) and in the long  
term (restenosis).

15 The mechanism of acute reocclusion appears to involve  
several factors and may result from vascular recoil with  
resultant closure of the artery and/or deposition of blood  
platelets along the damaged length of the newly opened  
blood vessel followed by formation of a fibrin/red blood  
cell thrombus. Recently, intravascular stents have been  
20 examined as a means of preventing acute reclosure after  
PTCA.

25 Restenosis (chronic reclosure) after angioplasty is a  
more gradual process than acute reocclusion: 30% of  
patients with subtotal lesions and 50% of patients with  
chronic total lesions will go on to restenosis after  
angioplasty. While the exact mechanism for restenosis is  
still under active investigation, the general aspects of  
the restenosis process have been identified:

30 In the normal arterial wall, smooth muscle cells  
(SMC) proliferate at a low rate ( $<0.1\%/day$ ; ref). SMC in  
vessel wall exists in a 'contractile' phenotype  
characterized by 80-90% of the cell cytoplasmic volume  
occupied with the contractile apparatus. Endoplasmic

5       reticulum, golgi bodies, and free ribosomes are few and  
located in the perinuclear region. Extracellular matrix  
surrounds SMC and is rich in heparin-like  
glycosylaminoglycans which are believed to be responsible  
for maintaining SMC in the contractile phenotypic state.

10       Upon pressure expansion of an intracoronary balloon  
catheter during angioplasty, smooth muscle cells within  
the arterial wall become injured. Cell derived growth  
factors such as platelet derived growth factor (PDGF),  
15       basic fibroblast growth factor (bFGF), epidermal growth  
factor (EGF), etc. released from platelets (i.e., PDGF)  
adhering to the damaged arterial luminal surface, invading  
macrophages and/or leukocytes, or directly from SMC (i.e.,  
BFGF) provoke a proliferation and migratory response in  
20       medial SMC. These cells undergo a phenotypic change from  
the contractile phenotype to a 'synthetic' phenotype  
characterized by only few contractile filament bundles but  
extensive rough endoplasmic reticulum, golgi and free  
ribosomes. Proliferation/migration usually begins within  
25       1-2 days post-injury and peaks at 2 days in the media,  
rapidly declining thereafter (Campbell et al., In:  
*Vascular Smooth Muscle Cells in Culture*, Campbell, J.H.  
and Campbell, G.R., Eds, CRC Press, Boca Ration, 1987, pp.  
39-55); Clowes, A.W. and Schwartz, S.M., *Circ. Res.*  
30       56:139-145, 1985).

Finally, daughter synthetic cells migrate to the  
intimal layer of arterial smooth muscle and continue to  
proliferate. Proliferation and migration continues until

5 the damaged luminal endothelial layer regenerates at which  
time proliferation ceases within the intima, usually  
within 7-14 days postinjury. The remaining increase in  
intimal thickening which occurs over the next 3-6 months  
is due to an increase in extracellular matrix rather than  
10 cell number. Thus, SMC migration and proliferation is an  
acute response to vessel injury while intimal hyperplasia  
is a more chronic response. (Liu et al., Circulation,  
79:1374-1387, 1989).

5 Patients with symptomatic reocclusion require either  
repeat PTCA or CABG. Because 30-50% of patients  
undergoing PTCA will experience restenosis, restenosis has  
clearly limited the success of PTCA as a therapeutic  
approach to coronary artery disease. Because SMC  
20 proliferation and migration are intimately involved with  
the pathophysiological response to arterial injury,  
prevention of SMC proliferation and migration represents a  
target for pharmacological intervention in the prevention  
of restenosis.

## 25 Summary of the Invention:

### Novel Features and Applications to Stent Technology

30 Currently, attempts to improve the clinical  
performance of stents have involved some variation of  
either applying a coating to the metal, attaching a  
covering or membrane, or embedding material on the surface  
via ion bombardment. A stent designed to include

5       reservoirs is a new approach which offers several  
important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

10       In this application, it is desired to deliver a  
therapeutic agent to the site of arterial injury. The  
conventional approach has been to incorporate the  
therapeutic agent into a polymer material which is then  
coated on the stent. The ideal coating material must be  
15       able to adhere strongly to the metal stent both before and  
after expansion, be capable of retaining the drug at a  
sufficient load level to obtain the required dose, be able  
to release the drug in a controlled way over a period of  
several weeks, and be as thin as possible so as to  
20       minimize the increase in profile. In addition, the  
coating material should not contribute to any adverse  
response by the body (i.e., should be non-thrombogenic,  
non-inflammatory, etc.). To date, the ideal coating  
material has not been developed for this application.

25       An alternative would be to design the stent to  
contain reservoirs which could be loaded with the drug. A  
coating or membrane of biocompatible material could be  
applied over the reservoirs which would control the  
30       diffusion of the drug from the reservoirs to the artery  
wall.

One advantage of this system is that the properties  
of the coating can be optimized for achieving superior

5 biocompatibility and adhesion properties, without the  
addition requirement of being able to load and release the  
drug. The size, shape, position, and number of reservoirs  
can be used to control the amount of drug, and therefore  
the dose delivered.

10 Description of the Drawings:

15 *a* The invention will be better understood in connection  
with the following figures in which Figures 1 and *1a* are  
top views and section views of a stent containing  
reservoirs as described in the present invention;

20 Figures 2a and 2b are similar views of an alternate  
embodiment of the stent with open ends;

25 Figures 3a and 3b are further alternate figures of a  
device containing a grooved reservoir; and

Figure 4 is a layout view of a device containing a  
reservoir as in Figure 3.

Detailed Description of the Invention

30 Pharmacological attempts to prevent restenosis by  
pharmacologic means have thus far been unsuccessful and  
all involve systemic administration of the trial agents.  
Neither aspirin-dipyridamole, ticlopidine, acute heparin  
administration, chronic warfarin (6 months) nor  
methylprednisolone have been effective in preventing  
restenosis although platelet inhibitors have been



5 effective in preventing acute reocclusion after  
angioplasty. The calcium antagonists have also been  
unsuccessful in preventing restenosis, although they are  
still under study. Other agents currently under study  
10 include thromboxane inhibitors, prostacyclin mimetics,  
platelet membrane receptor blockers, thrombin inhibitors  
and angiotensin converting enzyme inhibitors. These  
agents must be given systemically, however, and attainment  
of a therapeutically effective dose may not be possible;  
antiproliferative (or anti-restenosis) concentrations may  
15 exceed the known toxic concentrations of these agents so  
that levels sufficient to produce smooth muscle inhibition  
may not be reached (Lang et al., 42 Ann. Rev. Med., 127-  
132 (1991); Popma et al., 84 Circulation, 1426-1436  
(1991)).

20 Additional clinical trials in which the effectiveness  
for preventing restenosis of dietary fish oil supplements,  
thromboxane receptor antagonists, cholesterol lowering  
agents, and serotonin antagonists has been examined have  
25 shown either conflicting or negative results so that no  
pharmacological agents are as yet clinically available to  
prevent post-angioplasty restenosis (Franklin, S.M. and  
Faxon, D.P., 4 Coronary Artery Disease, 232-242 (1993);  
Serruys, P.W. et al., 88 Circulation, (part 1) 1588-1601,  
30 (1993).

Conversely, stents have proven useful in preventing  
reducing the proliferation of restenosis. Stents, such as  
the stent <sup>40</sup>~~10~~, seen in layout in Figure 4, balloon-

5 expandable slotted metal tubes (usually but not limited to  
stainless steel), which when expanded within the lumen of  
an angioplastied coronary artery, provide structural  
support to the arterial wall. This support is helpful in  
maintaining an open path for blood flow. In two  
10 randomized clinical trials, stents were shown to increase  
angiographic success after PTCA, increase the stenosed  
blood vessel lumen and to reduce the lesion recurrence at  
6 months (Serruys et al., 331 New Eng Jour. Med, 495,  
(1994); Fischman et al., 331 New Eng Jour. Med, 496-501  
15 (1994). Additionally, in a preliminary trial, heparin  
coated stents appear to possess the same benefit of  
reduction in stenosis diameter at follow-up as was  
observed with non-heparin coated stents. Additionally,  
heparin coating appears to have the added benefit of  
20 producing a reduction in sub-acute thrombosis after stent  
implantation (Serruys et al., 93 Circulation, 412-422,  
(1996). Thus, 1) sustained mechanical expansion of a  
stenosed coronary artery has been shown to provide some  
measure of restenosis prevention, and 2) coating of stents  
25 with heparin has demonstrated both the feasibility and the  
clinical usefulness of delivering drugs to local, injured  
tissue off the surface of the stent.

30 Numerous agents are being actively studied as  
antiproliferative agents for use in restenosis and have  
shown some activity in experimental animal models. These  
include: heparin and heparin fragments (Clowes and  
Karnovsky, 265 Nature, 25-626, (1977); Guyton, J.R. et al.  
46 Circ. Res., 625-634, (1980); Clowes, A.W. and Clowes,

5 M.M., 52 Lab. Invest., 611-616, (1985); Clowes, A.W. and  
Clowes, M.M., 58 Circ. Res., 839-845 (1986); Majesky et  
al., 61 Circ Res., 296-300, (1987); Snow et al., 137 Am.  
J. Pathol., 313-330 (1990); Okada, T. et al., 25  
10 Neurosurgery, 92-898, (1989) colchicine (Currier, J.W. et  
al., 80 Circulation, 11-66, (1989), taxol (ref),  
angiotensin converting enzyme (ACE) inhibitors (Powell,  
J.S. et al., 245 Science, 186-188 (1989), angiopeptin  
(Lundergan, C.F. et al., 17 Am. J. Cardiol. (Suppl. B);  
132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85  
5 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF  
antibody (Ferns, G.A.A., et al., 253 Science, 1129-1132  
(1991), terbinafine (Nemecek, G.M. et al., 248 J.  
Pharmacol. Exp. Thera., 1167-11747 (1989), trapidil (Liu,  
M.W. et al., 81 Circulation, 1089-1093 (1990), interferon-  
20 gamma (Hansson, G.K. and Holm, 84 J. Circulation, 1266-  
1272 (1991), steroids (Colburn, M.D. et al., 15 J. Vasc.  
Surg., 510-518 (1992), see also Berk, B.C. et al., 17 J.  
Am. Coll. Cardiol., 111B-1 17B (1991), ionizing radiation  
(ref), fusion toxins (ref) antisense oligonucleotides  
25 (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a  
macrolide antibiotic which blocks IL-2- mediated T-cell  
proliferation and possesses antiinflammatory activity.  
30 While the precise mechanism of rapamycin is still under  
active investigation, rapamycin has been shown to prevent  
the G<sub>1</sub> to S phase progression of T-cells through the cell  
cycle by inhibiting specific cell cyclins and cyclin-  
dependent protein kinases (Siekierka, Immunol. Res. 13:

5 110-116, 1994). The antiproliferative action of rapamycin  
is not limited to T-cells; Marx et al. (Circ Res 76:412-  
417, 1995) have demonstrated that rapamycin prevents  
proliferation of both rat and human SMC *in vitro* while  
10 Poon et al. have shown the rat, porcine, and human SMC  
migratin can also be inhibited by rapamycin (J Clin Invest  
98: 2277-2283, 1996). Thus, rapamycin is capable of  
inhibiting both the inflammatory response known to occur  
after arterial injury and stent implantation, as well as  
the SMC hyperproliferative response. In fact, the  
15 combined effects of rapamycin have been demonstrated to  
result in a diminished SMC hyperproliferative response in  
a rat femoral artery graft model and in both rat and  
porcine arterial balloon injury models (Gregory et al.,  
Transplantation 55:1409-1418, 1993; Gallo et al., in  
20 press, (1997)). These observations clearly support the  
potential use of rapamycin in the clinical setting of  
post-angioplasty restenosis.

25 Although the ideal agent for restenosis has not yet  
been identified, some desired properties are clear:  
inhibition of local thrombosis without the risk systemic  
bleeding complications and continuous and prevention of  
the dequale of arterial injury, including local  
inflammation and sustained prevention smooth muscle  
30 proliferation at the site of angioplasty without serious  
systemic complications. Inasmuch as stents prevent at  
least a portion of the restenosis process, an agent which  
prevents inflammation and the proliferation of SMC

5 combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

10 Agents: Rapamycin (sirolimus) structural analogs (macrocylic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

15 These can vary:

20 - Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

25 - or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

30 - or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour

5 deposition methods such as rf-plasma polymerization) and combinations thereof.

- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

10 - Extravascular delivery by the pericardial route

- Extravascular delivery by the advential application of sustained release formulations.

15 Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

20 prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method - Delivery from Polymer Matrix:

25 Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based  
30 polyesters or copolyesters, e.g., polylactide, polycaprolacton-glycolide, polyorthoesters, polyanhydrides; poly-aminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends

5        thereof. Nonabsorbable biocompatible polymers are also  
suitable candidates. Polymers such as polydimethyl-  
siloxane; poly(ethylene-vinylacetate); acrylate based  
polymers or copolymers, e.g., poly(hydroxyethyl  
methacrylate, polyvinyl pyrrolidinone; fluorinated  
10       polymers such as polytetrafluoroethylene; cellulose  
esters.

15       Polymer/drug mixture is applied to the surfaces of  
the stent by either dip-coating, or spray coating, or  
brush coating or dip/spin coating or combinations thereof,  
and the solvent allowed to evaporate to leave a film with  
entrapped rapamycin.

20       2. Experimental Stent Delivery Method - Delivery from  
Microporous Depots in Stent Through a Polymer Membrane  
Coating:

25       Stent, whose body has been modified to contain  
micropores or channels is dipped into a solution of  
Rapamycin, range 0.001 wt% to saturated, in organic  
solvent such as acetone or methylene chloride, for  
sufficient time to allow solution to permeate into the  
pores. (The dipping solution can also be compressed to  
improve the loading efficiency.) After solvent has been  
30       allowed to evaporate, the stent is dipped briefly in fresh  
solvent to remove excess surface bound drug. A solution  
of polymer, chosen from any identified in the first  
experimental method, is applied to the stent as detailed

5 above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method - Delivery via lysis of a Covalent Drug Tether

10 Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method - Pericardial Delivery

15 A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-glycolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10 $\mu$  to 25 1000 $\mu$ . The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

30 B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37°C, range 40°-45°C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the



5 vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in  
10 Figures 1a, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir or channel 11, 21, 31. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. Figure 4 shows a stent 40 with a reservoir 45  
15 created at the apex of a flexible strut. Of course, this reservoir 45 is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.  
20

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an  
25 effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

30 These and other concepts will be disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be

Year	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	